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POST-SERVICE MORTALITY OF AIR FORCE VETERANS OCCUPATIONALLY EXPOSED TO HERBICIDES DURING THE VIETNAM WAR: FINAL REPORT

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14. ABSTRACT

Since 1982, the Air Force Health Study has continued to assess the mortality of veterans of Operation Ranch Hand, the unit responsible for aerially spraying herbicides in Vietnam. The mortality of 1,263 Ranch Hand veterans to December 31, 2003 was contrasted with that of 19,080 Comparison veterans. The relative risk for all-cause mortality was significantly increased (RR=1.25, 95% Confidence Interval (CI): 1.1, 1.4, p<0.001). The risk of death caused by cancer was not significantly elevated (RR=1.1, 95% CI: 0.9, 1.4, p=0.39). The risk of death caused by circulatory system diseases was significantly increased in all occupations combined (RR=1.4, 95% CI: 1.1, 1.8, p=0.001) and in enlisted ground crew (RR=1.8, 95% CI: 1.3, 2.4, p<0.001), a subgroup with relatively high skin exposure to herbicides. Similarly increased risks of circulatory disease death in Ranch Hand personnel, particularly enlisted ground crew, were found among 2,758 veterans who attended physical examination. Among 2,551 veterans with dioxin assay results who attended physical examination, risk of death due to circulatory disease was significantly elevated for Ranch Hand veterans in the Low and High dioxin exposure categories (Low: RR=1.9, 95% CI:1.1,3.3, p=0.02; High: RR=2.3, 95% CI:1.3,4.0, p=0.005; trend: p<0.001).

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1. INTRODUCTION

The long-term effects of herbicide exposure on human health are not fully known and remain controversial. Herbicides were used by US forces in South Vietnam for defoliation during the Vietnam War. The toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), the contaminant found in Agent Orange and other herbicides sprayed during the war, continue to be of concern more than thirty years after the war. Studies of the post-service mortality experience of Vietnam veterans[1-7] have given mixed results. The US Army Chemical Corps study[1] reported an increased risk of death due to digestive diseases and a non-significant increase in the risk of death from cancer. A study of Australian Army veterans[4] reported an increased risk of death due to digestive diseases but no increases due to cancer. However, a study of women veterans[3] found an increased risk of death due to pancreatic cancer and a study of Vietnam veterans from Michigan[6] reported an excess of deaths due to non-Hodgkin's lymphoma.

Diverse results have been reported in numerous studies involving dioxin-exposed industrial workers[8-17] and a community exposed to dioxin from a nearby industrial accident[18-22]. One study of US chemical workers reported relative increases in mortality from all cancers combined and, in workers who survived more than 20 years since their exposure, increased mortality due to soft-tissue sarcoma and cancer of the respiratory system[9]. A different study of pentachlorophenol manufacturing workers found no excess risk of death due to cancer or all causes combined[13]. More than 15 years after an accidental explosion in a plant near Seveso, Italy exposed the surrounding community to kilogram amounts of dioxin, mortality among the most highly exposed men was significantly increased from all cancers, rectal cancer and lung cancer[18].

The Air Force Health Study (AFHS) is a prospective epidemiological study of the health[23-29], mortality[30-32],and reproductive outcomes[33-36] of veterans of Operation Ranch Hand, the unit responsible for aerially spraying herbicides in Vietnam from 1962 to 1971. The study began in 1982 and concludes in 2006. This report updates our mortality findings published in 2005 (deaths through December, 1999)[32] by summarizing current all-cause and cause-specific post-service mortality in veterans of Operation Ranch Hand to December 31, 2003.

2. MATERIALS AND METHODS

Population definition and the process by which mortality was determined were discussed in detail in our first mortality report[30]. We contrast cumulative Ranch Hand (N=1,263) post-service mortality through December 31, 2003 with that of a Comparison population of 19,080 Air Force veterans who flew or serviced C-130 cargo aircraft in Southeast Asia between 1962 and 1971, the same calendar period that the Ranch Hand unit was active in Vietnam. Comparison veterans were stationed throughout Southeast Asia, were not involved with spraying herbicides, and were demographically similar to Ranch Hand veterans. Veterans killed in action during the Vietnam War were excluded because Ranch Hand combat deaths were not caused by herbicide exposure. Twenty-two Ranch Hand and 109 Comparison veterans were killed in action in Vietnam. Since our last mortality report[32], one previously unidentified Ranch Hand was added to the AFHS and continued record review found tour information for two additional Comparisons, yielding 1263 Ranch Hand veterans, one more than previously reported, and 19,080 Comparison veterans, two more than previously reported[32]. All of the 20,343 veterans studied were male.

The numbers of veterans at risk are summarized in Table 1 by military occupation (pilots and navigators, administrative officers, enlisted flight crew, enlisted ground crew). All pilots and navigators were officers. We used military occupation as a surrogate to adjust for both socioeconomic status and inferred herbicide exposure. Most enlisted personnel were not college educated and most officers were college graduates. Dioxin assay results[23] suggest that, among Ranch Hand veterans, enlisted personnel were more heavily exposed than officers and, among enlisted veterans, ground crew were more heavily exposed than flight crew.

Table 1. Number of veterans by exposure group and military occupation among US Air Force veterans who served in Southeast Asia from 1962 to 1971.

Military Occupation	Ranch Hand	Comparison
Pilots and navigators	441	5,243
Administrative officers	26	284
Enlisted flight crew	209	2,828
Enlisted ground crew	587	10,725
All personnel	1263	19,080

Cohort contrasts not involving serum dioxin measurements

All 20,343 veterans were included. Veterans who survived to December 31, 2003, the cutoff date for these analyses, contributed the time, in years, between the dates of entry into follow-up (the date of the start of service in Southeast Asia) and the cutoff date, and those known to have died before the cutoff date contributed the time, in years, between the dates of entry into follow-up and death. We computed the relative risk (RR), a 95% confidence interval (CI) for the RR, and a p-value for testing the null hypothesis that RR=1 using a proportional hazards model with adjustment for birth year and military occupation. In one table, due to small numbers of deaths, we combined pilots, navigators and administrative officers into a single occupational category named "officers". We did not adjust for race because there were too few Blacks (6.2% of the Ranch Hand cohort) to permit adjustment. We classified underlying causes of death in accordance with the rules and conventions of the 9th revision of the International Classification of Diseases (ICD-9)[37]. Among the 20,343 veterans included in this mortality assessment, we were

unable to adjust for smoking, a risk factor for cardiovascular disease, or for drinking, a risk factor for liver disease, because risk factor information was available only for the subgroup of veterans who attended at least one physical examination[23].

To assess possible cancer latency, we conducted statistical analyses of death caused by cancer within 20 years and at least 20 years since the start of service in Southeast Asia. When considering deaths occurring within 20 years of service, all veterans were included. When considering deaths occurring at least 20 years since service in Southeast Asia, only those who survived 20 years from service were included.

Contrasts utilizing veterans who attended physical examination

These analyses were restricted to the 2,758 veterans who attended at least one physical examination administered in 1982, 1985, 1987, 1992, 1997 or 2002 (Ranch Hand: N=1,115, Comparison: N=1,643), adjusting for potential risk factors. We defined a pack-year as the equivalent of smoking one pack of cigarettes per day for one year. A drink-year was defined as the equivalent of drinking one 1.5 ounce of 80-proof alcoholic beverage per day for one year. Smoking and drinking data were taken from 1982, the year in which the first physical examinations were given. All-cause mortality was adjusted for military occupation, year of birth, smoking history (pack-years), drinking history (drink-years) and family history of heart disease. Cancer mortality was adjusted for military occupation, year of birth, smoking history, skin reaction to sun exposure (low, medium, high) and eye color (brown, hazel/green, gray/blue). We

adjusted circulatory disease mortality for military occupation, year of birth, smoking history and family history of heart disease.

Contrasts utilizing serum dioxin measurements

Dioxin assays have been administered to 1032 (93%) of the 1,115 Ranch Hands and 1,531 (93%) of the 1,643 Comparisons who attended physical examination. Table 2 shows a cross classification of all Ranch Hands and Comparisons by survival status (dead, alive), assay status (yes, no) and result comment.

Table 2

Dioxin Assay Status versus Survival among Veterans Who Attended Physical Examination

Dioxin	Result	Ranch Hand			Comparison		
Assay	Comment[a]	Alive	Dead	Total	Alive	Dead	Total
No		40	43	83	54	58	112
Yes	G	887	119	1,006	1,162	142	1,304
	GND	17[b]	3	20	194	16	210
	GNQ	0	2	2	7	3	10
	NR	1	3	4	4	3	7
Total		945	170	1,115	1,421	222	1,643

[a]G, Good result
GND, Good result, below limit of detection
GNQ, Good result, below limit of quantitation
NR, No result

[b]One veteran with a GND result had missing lipids and therefore no lipid-adjusted dioxin assay results

These analyses were restricted to the 2,551 veterans who attended at least one physical examination administered in 1982, 1985, 1987, 1992, 1997 or 2002 and who received a dioxin assay result (Ranch Hand: N=1,027, Comparison: N=1,524). These analyses were adjusted for the same potential risk factors described previously for analysis of veterans who attended physical examination.

Dioxin levels were measured in parts per trillion (ppt) on a lipid weight basis in serum collected from veterans who completed the 1987 physical examination[38-39]. Additional measurements were made in 1992, 1997 and 2002. For those veterans whose dioxin level was not measured in 1987, the subsequent measure was extrapolated to 1987 using a first-order kinetics model with a constant half-life of 7.6 years[40]. Non-detectable or "GND" (non-quantitable or "GNQ") dioxin levels were replaced by the value of the limit of detection (limit of quantitation) divided by $\sqrt{2}$ [41].

Among the 1263 Ranch Hand veterans, 231 never had blood drawn for the dioxin assay and were excluded from dioxin analysis. Of the remaining 1032, four Ranch Hands had an assay result of "NR" or "No Result", while one Ranch Hand had a blood draw with missing lipid results and therefore missing lipid-adjusted dioxin results. After these exclusions, 1027 Ranch Hands (903 living, 124 dead) remained for dioxin analysis.

We assigned each veteran to one of four dioxin exposure categories based on his cohort (Ranch Hand, Comparison), dioxin concentration, and half-life extrapolated initial dioxin concentration. Comparison veterans with a dioxin measurement were assigned to the

"Comparison" category. Ranch Hand veterans with a dioxin measurement not exceeding 10 ppt were assigned to the "Background" category. Ranch Hand veterans with dioxin levels exceeding 10 ppt had their initial dioxin at the end of service in Vietnam estimated using a first-order kinetics model with a constant half-life of 7.6 years. Among Ranch Hand veterans with a dioxin body burden exceeding 10 ppt, those with an initial dioxin less than or equal to 117.6 ppt (the median initial dioxin in this subgroup) were assigned to the "Low" category and those with an initial dioxin greater than 117.6 ppt were assigned to the "High" category.

We report deaths from all causes, cancer and circulatory disease, and the associated RR, 95% CI and p-value, for contrasting each of the three Ranch Hand dioxin exposure categories with the Comparison category, based on a proportional hazards model. Survival time for dead veterans was the time in years between the beginning of their tour in Vietnam (Ranch Hands), or qualifying tour in Southeast Asia (Comparisons), and death. For living veterans, survival time was the time, in years, between the beginning of their tour of duty in Vietnam (Ranch Hands), or qualifying tour in Southeast Asia (Comparisons), and 31 December 2003. We reported the p-value for trend, for the test of the hypothesis that the coefficient of the log-transformed serum dioxin concentration was equal to 1.0 in the combined cohort.

A separate analysis using continuous dioxin, rather than dioxin category, was conducted. An accelerated failure time model for right-censored survival data was fitted to assess the relationship, if any, between survival time and the logarithm of dioxin level in Ranch Hands. The dependent variable was the logarithm of survival time and the independent variable was the logarithm of dioxin.

3. RESULTS

Table 3 presents demographic characteristics of all veterans. Relatively more Ranch Hand veterans were pilots or navigators (34.9%) than Comparison veterans (27.5%) and more Comparison veterans were enlisted ground crew (56.2%) than Ranch Hand veterans (46.5%). The two cohorts were similar with regard to the median (range) birth year (Ranch Hand: 1938 (1911 to 1950), Comparison: 1942 (1907 to 1952)).

Table 3. Distribution of demographic characteristics of 20,343 US Air Force veterans who served in Southeast Asia from 1962 to 1971.

	Percent	
Characteristic	Ranch Hand	Comparison
Black	6.2	6.9
Military Occupation:		
Pilots and navigators	34.9	27.5
Administrative officers	2.1	1.5
Enlisted flight crew	16.5	14.8
Enlisted ground crew	46.5	56.2

Cohort contrasts not involving serum dioxin measurements

Ranch Hand and Comparison mortality is summarized in Table 4. Two hundred forty of 1,263 (19.0%) Ranch Hand veterans and 2,734 of 19,080 (14.3%) Comparison veterans died from all causes during the post-service period through 2003; the all-cause relative risk of death was significantly increased (RR=1.25, 95% CI: 1.1, 1.4, $p<0.001$). The relative risk of death from diseases of the circulatory system was significantly increased (RR=1.4, 95% CI: 1.1, 1.8, $p=0.001$), based on 89 Ranch Hand and 874 Comparison deaths. The relative risk of death from cancer was not significantly increased (RR=1.1, 95% CI: 0.9, 1.4, $p=0.38$), based on 68 Ranch Hand and 854 Comparison deaths. The relative risks of death caused by diseases of the respiratory, digestive and endocrine systems were non-significantly increased based on small numbers of Ranch Hand deaths (10, 12 and 7 respectively).

All-cause mortality and mortality due to cancer and circulatory diseases are summarized in Table 5 by military occupation. The relative risk of death from any cause was significantly increased among enlisted ground crew (RR=1.4 95% CI: 1.1, 1.7, $p=0.001$) mostly due to a significant increase in the risk of death caused by diseases of the circulatory system (RR=1.8, 95% CI: 1.3, 2.4, $p<0.001$).

Table 4. Cause-specific and all-cause mortality of 20,343 US Air Force veterans who served in Southeast Asia from 1962 to 1971.

	Number of Deaths (%)				
Cause of Death[a]	Ranch Hand	Comparison	RR	95% CI	p-value
All causes	240 (19.0)	2734 (14.3)	1.25	1.1, 1.4	<0.001
Infectious or parasitic diseases	2 (0.2)	29 (0.2)	1.0	0.2, 4.0	0.96
Cancer	68 (5.4)	854 (4.5)	1.1	0.9, 1.4	0.38
Endocrine diseases	7 (0.6)	46 (0.2)	2.2	1.0, 4.9	0.05
Nervous system diseases	2 (0.2)	54 (0.3)	0.5	0.1, 2.1	0.34
Genitourinary diseases	1 (0.1)	20 (0.1)	0.7	0.1, 5.4	0.76
Circulatory diseases	89 (7.0)	874 (4.6)	1.4	1.1, 1.8	0.001
Respiratory diseases	10 (0.8)	126 (0.7)	1.1	0.6, 2.1	0.74
Digestive diseases	12 (0.9)	101 (0.5)	1.7	0.9, 3.0	0.10
Ill Defined or Unknown	10 (0.8)	92 (0.5)	1.8	0.9, 3.4	0.09
Accident	31 (2.4)	370 (1.9)	1.2	0.9, 1.8	0.26
Suicide	5 (0.4)	113 (0.6)	0.7	0.3, 1.6	0.38
Homicide	3 (0.2)	27 (0.1)	1.8	0.5, 5.8	0.36

[a] All causes (ICD 001-969), Infectious or parasitic diseases (001-139), Cancer (140-208, 230-234), Endocrine diseases (240-279), Nervous system diseases (320-389), Genitourinary diseases (580-629), Circulatory diseases (390-459), Respiratory diseases (460-519), Digestive diseases (520-579), Ill-defined or unknown (780-799), Accident (800-949), Suicide (950-959), Homicide (960-969).

Table 5. All-cause, cancer, and circulatory disease mortality by military occupation for 20,343 US Air Force veterans who served in Southeast Asia from 1962 to 1971.

		Number of Deaths (%)				
Cause of Death	Military Occupation	Ranch Hand	Comparison	RR	95% CI	p-value
All Causes	Pilots and navigators	79 (17.9)	826 (15.7)	1.2	0.9, 1.5	0.17
	Administrative officers	7 (26.9)	57 (20.1)	1.8	0.8, 4.0	0.15
	Enlisted flight crew	46 (22.0)	493 (17.4)	1.0	0.7, 1.3	0.86
	Enlisted ground crew	108 (18.4)	1358 (12.7)	1.4	1.1, 1.7	0.001
Cancer	Pilots and navigators	26 (5.9)	288 (5.5)	1.1	0.7, 1.7	0.58
	Administrative officers	1 (3.8)	19 (6.7)	0.7	0.1, 5.2	0.72
	Enlisted flight crew	18 (8.6)	159 (5.6)	1.1	0.7, 1.9	0.58
	Enlisted ground crew	23 (3.9)	388 (3.6)	1.0	0.6, 1.5	0.94

Table 5. (Continued).

Cause of Death	Military Occupation	Number of Deaths (%) Ranch Hand	Comparison	RR	95% CI	p-value
Circulatory	Pilots and navigators	26 (5.9)	254 (4.8)	1.3	0.9, 2.0	0.19
disease	Administrative officers	2 (7.7)	18 (6.3)	1.6	0.4, 6.8	0.55
	Enlisted flight crew	12 (5.7)	149 (5.3)	0.8	0.5, 1.5	0.49
	Enlisted ground crew	49 (8.3)	453 (4.2)	1.8	1.3, 2.4	<0.001

Table 6 summarizes cancer mortality by time since service in Southeast Asia (less than 20 years, at least 20 years) and military occupation. Twelve of 68 Ranch Hand cancer deaths (18%) occurred within the first 20 years from service in Southeast Asia, while the remaining 56 (82%) occurred at least 20 years after service in Southeast Asia. The relative risk of death from cancer was not significantly increased among veterans who survived at least 20 years after service in Southeast Asia (RR=1.2, 95% CI: 0.9, 1.5) and the relative risks among officers (RR=1.2), enlisted flight crew (RR=1.2) and enlisted ground crew (RR=1.1) were not significantly increased. The relative risk of death caused by cancer among veterans within 20 years of their service in Southeast Asia was not increased in any of the three occupational strata.

Table 6. Cancer mortality by time since service in Southeast Asia and military occupation among US Air Force veterans who served in Southeast Asia from 1962 to 1971.

a) Cancer deaths within 20 years of start of service in Southeast Asia

	Number of Deaths (%)				
Military Occupation	Ranch Hand	Comparison	RR	95% CI	p-value
Officers	5 (1.1)	76 (1.4)	0.8	0.3, 2.0	0.62
Enlisted flight crew	3 (1.4)	31 (1.1)	1.0	0.3, 3.3	0.99
Enlisted ground crew	4 (0.7)	87 (0.8)	0.7	0.3, 2.0	0.52
All personnel	12 (0.9)	194 (1.0)	0.8	0.5, 1.5	0.52

b) Cancer deaths at least 20 years after start of service in Southeast Asia

	Number of Deaths (%)				
Military Occupation	Ranch Hand	Comparison	RR	95% CI	p-value
Officers	22 (4.9)	231 (4.4)	1.2	0.8, 1.9	0.39
Enlisted flight crew	15 (7.6)	128 (4.8)	1.2	0.7, 2.0	0.55
Enlisted ground crew	19 (3.4)	301 (2.9)	1.1	0.7, 1.7	0.79
All personnel	56 (4.7)	660 (3.6)	1.2	0.9, 1.5	0.26

Cancer deaths by primary anatomical site were enumerated (data not shown); those sites with at least five Ranch Hand deaths were statistically analyzed. Of the deaths caused by cancer (Ranch Hand: 68, Comparison: 854), the majority was caused by cancers of the bronchus and lung (Ranch Hand: 30, Comparison: 321), and most of those occurred among veterans who survived at least 20 years since their service in Southeast Asia (Ranch Hand 27, Comparison: 254; RR=1.4, 95% CI: 1.0, 2.1, p=0.08). The relative risk of death from cancer of the bronchus and lung was significantly increased among officers who survived at least 20 years since their service, based on 13 Ranch Hand and 91 Comparison deaths (RR=1.8, 95% CI: 1.0, 3.3, p=0.04). There were five Ranch Hand deaths due to pancreatic cancer which resulted in an elevated, but nonsignificant, relative risk of death (RR=2.1, 95% CI: 0.8,5.4, p=0.12). The numbers of Ranch Hand deaths caused by cancers at many other specific sites were less than or equal to 1; more than one, however, was caused by cancer of the stomach (N=3), prostate (N=2), kidney (N=2), brain (N=3), colon (N=2),and unspecified malignant neoplasms (N=4).

One Ranch Hand enlisted ground veteran died of non-Hodgkin's lymphoma 23.9 years after his service in Southeast Asia began. Three Ranch Hand veterans died of multiple myeloma, one was an enlisted flight crew veteran who died 24.2 years after his service, one an enlisted ground veteran who died 26.2 years after his service in Southeast Asia, and the other a pilot who died 40.2 years after his service. Two Ranch Hands died of soft-tissue sarcoma, one was a pilot who died 19.8 years after his service, and the other was an enlisted ground veteran who died 32.7 years after his service in Southeast Asia. One pilot died from myeloid leukemia 28.2 years after his service in Southeast Asia. No Ranch Hand deaths were caused by Hodgkin's disease or lymphoreticulosarcoma.

We grouped deaths caused by circulatory disease into 5 categories and contrasted enlisted ground Ranch Hand and Comparison mortality by category (Table 7); 34 of 49 Ranch Hand enlisted ground crew deaths (69.0%) were caused by atherosclerotic heart disease (RR=1.8, 95% CI: 1.3, 2.6, p=0.001). Not shown in Table 7, acute myocardial infarction (ICD-9 code 410) was the most common cause among enlisted ground crew who died from circulatory disease, accounting for 14 Ranch Hand and 186 Comparison deaths; RR=1.2, 95% CI: 0.7, 2.1, p=0.43. The second most common cause was coronary atherosclerosis (ICD-9 code 414), accounting for 9 Ranch Hand and 82 Comparison deaths (RR=1.9, 95% CI: 0.9, 3.7, p=0.07).

Table 7. Circulatory disease deaths by category in 11,312 enlisted ground crew among US Air Force veterans who served in Southeast Asia from 1962 to 1971.

	Number of Deaths (%)				
Category[a]	Ranch Hand	Comparison	RR	95% CI	p-value
Atherosclerotic heart disease	34 (5.8)	316 (2.9)	1.8	1.3,2.6	0.001
Cardiomyopathy	2 (0.3)	39 (0.4)	0.9	0.2, 3.6	0.83
Cerebrovascular disease	5 (0.8)	38 (0.3)	2.0	0.8, 5.2	0.14
Hypertensive disease	3 (0.5)	20 (0.2)	2.6	0.8, 8.8	0.12
Other circulatory diseases	5 (0.8)	40 (0.4)	2.1	0.8, 5.4	0.11
Total	49 (8.3)	453 (4.2)	1.8	1.3, 2.4	<0.001

a Atherosclerotic heart disease (ICD 410, 411, 412, 4140, 4148, 4149, 4284, 4409, 444), Cardiomyopathy (4254, 4255, 4280, 4289, 4239, 4263, 4274), Cerebrovascular disease (430, 431, 4329, 4340, 4349, 436, 4428, 4379), Hypertensive disease (4019, 4029, 4039, 4372, 4410, 4411, 4412, 4413, 4415), Other circulatory diseases (39890, 4151, 4160, 4169, 4241, 4249, 4273, 4275, 4279, 4292, 4293, 4299, 4414, 4416, 4439, 4460, 4462, 4560, 4590).

Contrasts utilizing veterans who attended physical examination

All-cause mortality and mortality due to cancer and circulatory diseases among AFHS veterans who attended at least one physical examination, regardless of dioxin assay status, are summarized in Table 8. Among Ranch Hand veterans, after adjustment for risk factors, the risk of death from all causes was not significantly elevated (RR=1.1) and the risk of death from cancer was not significantly decreased (RR=0.9). Ranch Hand deaths caused by circulatory disease were significantly increased (RR=1.5, 95% CI: 1.1,2.1, p=0.02), mainly due to elevated risk of circulatory disease death among enlisted ground crew (RR=1.9, 95% CI: 1.1,3.1, p=0.02).

Table. 8 Mortality of 2,758 US Air Force Veterans who attended physical examination.

a) Deaths from all causes

	Number of deaths (%)	RR[a]	95% CI	p-value
Comparison	222 (13.5)			
Ranch Hand	170 (15.2)	1.1	0.9, 1.4	0.29

b) Deaths caused by cancer

	Number of deaths (%)	RR[b]	95% CI	p-value
Comparison	89 (5.4)			
Ranch Hand	53 (4.7)	0.9	0.6, 1.3	0.68

c) Deaths caused by circulatory disease

	Number of deaths (%)	RR[c]	95% CI	p-value
Comparison	66 (4.0)			
Ranch Hand	67 (6.0)	1.5	1.1, 2.1	0.02

d) Enlisted Ground Crew Deaths caused by circulatory disease

	Number of deaths (%)	RR[d]	95% CI	p-value
Comparison	26 (3.4)			
Ranch Hand	32 (6.3)	1.9	1.1, 3.1	0.02

[a]Adjusted for military occupation, birth year, smoking, drinking and family history of heart disease.
[b]Adjusted for military occupation, birth year, smoking, reaction to sun exposure and eye color.
[c]Adjusted for military occupation, birth year, smoking, and family history of heart disease.
[d]Adjusted for birth year, smoking, and family history of heart disease.

Contrasts utilizing serum dioxin measurements

Table 9 presents demographic characteristics of the subgroup of veterans who had dioxin assay results and who attended at least one physical examination. Ranch Hand veterans in the High category were predominantly enlisted ground crew (76.4%) while those in the Background category were predominantly officers (57.1%). Ranch Hand veterans in the High category were younger than those in the Background or Low category.

Of the 124 deceased Ranch Hands with usable dioxin results, 5 died of digestive disease, 40 died of malignant neoplasms, 50 died of circulatory disease, 8 died of respiratory disease, 5 died of endocrine disorders, 2 died of nervous system disease, 1 died of genitourinary disease, 5 died of accidents, 2 committed suicide and 6 died of unknown or ill-defined conditions. After adjustment for year of birth, military occupation, smoking, drinking and family history of heart disease, an accelerated failure time model analysis found no association between dioxin level and survival time among Ranch Hands who died from all causes combined($p=0.82$). However, when Ranch Hand deaths were restricted to those due to circulatory disease, the same analysis found that higher dioxin levels were significantly associated with shorter times to death ($p=0.03$) (data not shown).

All-cause mortality and mortality due to cancer and circulatory diseases, adjusted for risk factors, are summarized in Table 10 by dioxin exposure category. No significant increase in the relative risk of death from all causes combined was observed (Background: RR= 1.0, Low: RR= 1.2, High: RR= 1.3; trend=0.07) (Table 10a). Table 10b shows decreased risk of death

from cancer in the Low and High dioxin categories. Deaths due to circulatory disease (Table 10c) were significantly increased in the Low category (RR=1.9, 95% CI 1.1,3.3, p=0.02), and in the High category (RR=2.3, 95% CI 1.3,4.0, p=0.005), resulting in a significant increasing trend ($p<0.001$).

Table 9. Demographic characteristics of 2,551 US Air Force veterans with dioxin assay results who attended at least one physical examination.

a) Median (range) serum dioxin, birth year, pack-years and drink-years

Characteristic	Comparison N=1524	Background N=452	Low N=287	High N=288
Serum dioxin[a]	3.8 (0.4-54.8)	5.6 (0.4-10.0)	15.0 (10.0-29.2)	47.5 (18.0-617.8)
Initial dioxin[b]	--	--	65.0 (32.2-117.4)	245.5 (117.9-4221.9)
Birth Year	1939 (1914-1950)	1937 (1913-1950)	1936 (1916-1950)	1945 (1916-1950)
Pack Years	10.7 (0-116)	10.7 (0-104)	13.1 (0-115)	10.5 (0-139)
Drink Years	12.5 (0-627)	11.2 (0-518)	14.1 (0-411)	10.5 (0-507)

[a] Measured in 1987, 1992, 1997 or 2002, parts per trillion in serum lipid. [b] Serum dioxin extrapolated to end of service in Vietnam, in parts per trillion in serum lipid.

Table 9. (Continued)

b) Family history of heart disease, race and military occupation (%)

Characteristic	Comparison N=1524	Background N=452	Low N=287	High N=288
Family History of Heart Disease	27.4	26.1	28.9	34.7
Black	6.6	5.1	8.4	4.9
Military Occupation:				
Pilots and navigators	35.8	57.1	36.6	2.4
Administrative officers	2.2	3.1	1.7	0.4
Enlisted flight crew	16.0	12.6	20.9	20.8
Enlisted ground crew	46.0	27.2	40.8	76.4

Table 10. Mortality of 2,551 US Air Force Veterans with dioxin assay results who attended physical examination.

a) Deaths from all causes

	Number of deaths (%)	RR[a]	95% CI	p-value
Comparison	161(10.6)			
Background	51 (11.3)	1.0	0.8, 1.4	0.81
Low	38 (13.2)	1.2	0.8, 1.7	0.35
High	35 (12.1)	1.3	0.9, 2.0	0.12

b) Deaths caused by cancer

	Number of deaths (%)	RR[b]	95% CI	p-value
Comparison	64 (4.2)			
Background	21 (4.6)	1.0	0.6, 1.7	0.95
Low	11(3.8)	0.8	0.4, 1.5	0.42
High	8 (2.8)	0.9	0.4, 1.9	0.74

Table 10. (Continued)

c) Deaths caused by circulatory disease

	Number of deaths (%)	RR[c]	95% CI	p-value
Comparison	47 (3.1)			
Background	14 (3.1)	1.0	0.6, 1.9	0.96
Low	18 (6.3)	1.9	1.1, 3.3	0.02
High	18 (6.3)	2.3	1.3, 4.0	0.005

[a]Adjusted for military occupation, birth year, smoking, drinking and family history of heart disease. Trend: p=0.07.
[b]Adjusted for military occupation, birth year, smoking, reaction to sun exposure and eye color. Trend: p=0.66
[c]Adjusted for military occupation, birth year, smoking, and family history of heart disease. Trend: p<0.001.

4. DISCUSSION

An evaluation of all-cause post-service mortality through December 31, 2003 found an increased relative risk that was significant (RR=1.25, 95% CI: 1.1,1.4, p<0.001) and a significant increase in the risk of death from diseases of the circulatory system in Ranch Hand enlisted ground crew, the subgroup with the highest dioxin levels (RR=1.8,, 95% CI: 1.3,2.4, p<0.001). This result agrees with our last report[32] which also showed an all-cause relative risk that exceeded 1.0. Prior to that report, this[30, 31] and other veteran's studies[1, 2, 4, 5] found either no increase or a deficit of deaths among those veterans presumed exposed.

The relative risk of death due to cancer was 1.1 (p=0.38), a result consistent with the Army Chemical Corp study[1], the CDC Vietnam Experience Study[2] and a Department of Veterans Affairs study of Army and Marine veterans[3]. These results are inconsistent with several industrial study cohorts, all of which found increases in cancer mortality among exposed workers. A US study of workers at 12 chemical plants that made dioxin-contaminated products[9] and a study of German workers exposed after a reactor accident[10] found excess mortality from cancer 20 or more years after the first exposure. Factory workers in Hamburg, Germany exhibited a dose-dependent relation between cancer mortality and exposure to dioxin[12]. A Dutch cohort of herbicide-manufacturing workers[14] was found to have increased cancer mortality. Results of the IARC industrial cohort study showed significantly increased mortality from all cancers combined among dioxin-exposed workers[17]. The Ranch Hand exposures were probably higher than many other Vietnam veterans, but were not as great as those among industrial cohorts. The median initial dose among Ranch Hand veterans with dioxin levels above

background was approximately 120 ppt, about one-tenth of the median predicted dose among workers in the NIOSH study[9].

To examine cancer mortality in a way that accounts for latency, some studies evaluate relative risk among those subjects who survived at least 20 years after entry into follow-up[9, 10]. Our analysis found a non-significant increase in the relative risk of death from cancer among veterans who survived at least 20 years since their service in Southeast Asia and, as expected, a non-significant decrease in the relative risk within 20 years of service in Southeast Asia.

We studied cancer deaths according to the primary anatomic site and found a non-significant increase in the relative risk of death caused by cancer of the bronchus and lung among veterans who survived at least 20 years after their service in Southeast Asia. Although not significant, the increase was consistent with increases in respiratory cancer mortality in three industrial cohorts surviving 20 years of follow-up[9, 10, 14]. Deaths caused by non-Hodgkin's lymphoma, Hodgkin's disease, myeloid leukemia or lymphoreticulosarcoma were too few to analyze.

At the examinations in 2002, Ranch Hand enlisted ground crew did not exhibit an increased prevalence of essential hypertension, heart disease (excluding essential hypertension), myocardial infarction, stroke, or transient ischemic attack, determined by medical record review, and a panel of non-invasive clinical measurements found no significant adverse effect[42]. Nevertheless, an association between dioxin exposure and cardiovascular diseases appears biologically plausible because dioxin and related compounds have the potential to cause an

increase of TGF-β1 in mammalian cells[43], which is known to induce fibrosis in a multitude of organs, including the heart, in animals[44, 45].

The increased risk of death caused by diseases of the circulatory system in Ranch Hand enlisted ground crew is consistent with several industrial cohort studies. An increased risk of death from ischemic heart disease (ICD-9 codes 410 to 414) was found in a study of exposed industrial workers at a Hamburg, Germany plant[12], a Dutch cohort of workers involved in herbicide production[14], a large US cohort study of chemical plant workers[15], and in the IARC international cohort study[17]. In the Hamburg study[12], the increased risk was dose-related. In this study, the relative risk of death from ischemic heart disease in Ranch Hand enlisted ground crew (Ranch Hand: 30, Comparison: 285) was significantly increased (RR=1.7, 95% CI: 1.2, 2.5, p=0.004). No significant increase in the relative risk of death from diseases of the circulatory system was found in two studies of US Army veterans[1, 2] or a study of Australian Army veterans[4]; the relative risk of death from ischemic heart disease was not reported in any of these three veterans' studies.

Dioxin assay results for 2,551 veterans who attended at least one physical examination allow a unique opportunity to assess possible dose-related effects of dioxin on the mortality of Vietnam veterans. Veterans in the Low and High dioxin categories had elevated risk of death from all causes but the trend was nonsignificant. No trend was observed for the decreased risk of cancer death in the Low and High dioxin categories, but a significantly increased risk of death due to circulatory disease was observed in the Low (RR=1.9) and High (RR=2.3) categories, resulting in a significant increasing trend with dioxin ($p<0.001$). These findings were consistent

with increased risk of death from circulatory disease in Ranch Hand enlisted ground crew because the Low and High categories comprise 75% of the dioxin-assayed Ranch Hand enlisted ground crew.

By design, both Ranch Hand and Comparison cohorts were comprised of veterans of the Vietnam War, precluding assessment of a Vietnam effect and limiting interpretations of cohort contrasts. A recent analysis of cancer mortality with adjustment for years spent in the SEA region and the percentage of SEA service spent in Vietnam found no significant increase in the risk of cancer death relative to US national rates[46], however, all site cancer, as defined by the Surveillance, Epidemiology and End Results (SEER) section of the National Cancer Institute, prostate cancer and melanoma cancer incidence was found to increase with dioxin category among Ranch Hand veterans who spent less than two years in the Southeast Asia region. Additionally, all site SEER cancer incidence was found to increase with dioxin exposure in Ranch Hand veterans who spent 100% of their SEA service in Vietnam.

Inconsistencies with industrial cohort study findings may reflect Ranch Hand initial dioxin doses 10 times less than predicted doses among factory worker cohorts in the U.S or Europe. Although Ranch Hand exposures were probably higher than that of other Vietnam veterans, they were not as high, and of shorter duration (generally one year), when compared to industrial cohorts. This study was not able to address the effect of major confounders on all-cause and cause-specific mortality among the entire cohort of 20,343 veterans because risk factor information, such as smoking, drinking and family history of disease was available only for the 2,758 veterans who have participated in the physical examinations to date, however results from

those who attended physical examinations suggest that the two groups are similar with regard to these risk factors. Our interpretations were limited by small numbers of deaths; increased relative risks based on small numbers of deaths had wide confidence intervals and were sensitive to an additional death in either cohort. The study is limited by its sample size, the lack of risk factor measurements in the entire Comparison cohort, and the relatively (compared to industrial cohorts) moderate dioxin body burdens in Ranch Hand veterans.

The strengths of this study included a large comparison population demographically similar to the Ranch Hand group and complete determination of the mortality status of all subjects. Over 2000 study veterans have had serum dioxin levels measured enabling assessment of dose-response relationships between dioxin and mortality. Among Vietnam veterans, the Ranch Hand unit is one of the few well-defined cohorts with demonstrably increased serum dioxin levels. Thus, this study offered the best available opportunity to address a hypothetical relation between herbicide exposure and mortality in Vietnam veterans.

In conclusion, an analysis of all-cause and cause-specific mortality through December 31, 2003 found a significantly increased risk of death from all causes in Ranch Hand veterans, and a significant increase in the risk of death from diseases of the circulatory system. A suggestive increase in the risk of lung cancer death among officers was found, but overall risk of cancer death was not significantly elevated. The risk of death attributable to circulatory system diseases, first observed to be significantly increased in the 1991 mortality update[47] (deaths through December 1989), continues to be increased, especially for enlisted ground crew, the subgroup with the highest dioxin levels. Similar significant elevations in the risk of circulatory system

disease death were seen among the subgroup of veterans who attended physical examination. Among those veterans who attended examination and who were also assayed for dioxin, a significant increasing trend in the risk of death due to circulatory system disease was observed as dioxin level increased.

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